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RCE
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# Request For Continued Examination (RCE) Transmittal

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| Application Number | 09/945,166 |
| Filing Date | August 31, 2001 |
| First Named Inventor | Elmaleh, David R. |
| Art Unit | 1635 |
| Examiner Name | Vivlemore, T. A. |
| Attorney Docket Number | FLA-003.01 |

**This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.**
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 C.F.R. 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

a. ☒ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
ii. ☒ Other: Consider the Amendment and Response to the Office Action mailed August 24, 2005 filed October 24, 2005

b. ☒ Enclosed

i. ☐ Amendment/Reply
ii ☐ Affidavit(s)/Declaration(s)
iii. ☐ Information Disclosure Statement (IDS)
iv. ☒ Other: Copy of Amendment and Response filed October 24, 2005; Return Receipt Postcard

2. Miscellaneous

a. ☐ Suspension of action on the above-identified application is requested under 37 C.F.R. 1.103(c) for a period of _____months. (Period of suspension shall not exceed 3 months; Fee under 37 C.F.R. 1.17(i) required)

b. ☐ Other _____

3. Fees The RCE fee under 37 C.F.R. 1.17(e) is required by 37 C.F.R. 1.114 when the RCE is filed.

a. ☒ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 06-1448 . ***I have enclosed a duplicate copy of this sheet.***

i. ☒ RCE fee required under 37 C.F.R. 1.17(e) **($395.00 for a Small Entity)**
ii. ☐ Extension of time fee (37 C.F.R. 1.136 and 1.17)
iii. ☐ Other _____

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b. ☐ Check in the amount of $ _____ enclosed
c. ☐ Payment by credit card (Form PTO-2038 enclosed)

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

***SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED***

| | | | |
|---|---|---|---|
| Signature | | Date | November 23, 2005 |
| Name (Print /Type) | Jennifer R. Zarutskie | Registration No. (Attorney/Agent) | 50,558 |

***CERTIFICATE OF MAILING OR TRANSMISSION***

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

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|---|---|---|---|
| Signature | Kristen Salera | | |
| Name (Print /Type) | Kristen Salera | Date | November 23, 2005 |

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re Application of: Elmaleh et al. | Attorney Docket No.: FLA-003.01 |
| Serial No.: 09/945,166 | Art Unit: 1635 |
| Filing Date: August 31, 2001 | Examiner: Tracy Ann Vivlemore |
| For: *Targeted Nucleic Acid Constructs and Uses Related Thereto* | |



**CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)**

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail, postage prepaid, in an envelope addressed to: Mailstop: AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

October 24, 2005
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Katelyn Nelson

Mailstop: AF
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## AMENDMENT AND RESPONSE

Dear Madam,

In response to the Office Action, mailed August 24, 2005, in the above-identified application, Applicants submit the following remarks and amendments in this request for reconsideration. Applicants respectfully request entry of the following claim amendments, because they present the claims in better form for consideration and do not present new issues requiring a search. No fee is believed to be due in connection with this submission. The Commissioner is hereby authorized to charge any deficiencies to Deposit Account Number **06-1448, Reference FLA- 003.01**.

**In the claims:**

Please amend the claims as follows:

1. **(Currently Amended)** A targeted oligonucleotide construct comprising: a targeting moiety which localizes to a site in an organism; an oligonucleotide complementary to a nucleic acid of interest; and an imaging agent suitable for use in Positron Emission Tomography (PET), Single Photon Emission Tomography (SPECT) or Magnetic Resonance Imaging (MRI), wherein the targeting moiety is selected from an antibody, a lectin, a ligand, a sugar, a steroid, a hormone, a nutrient, a small molecule and a protein, and wherein said targeted oligonucleotide construct has essentially no ability to cross the blood/brain barrier.

2. **(Previously Presented)** A targeted oligonucleotide construct as in claim 1, wherein said imaging agent is selected from the group consisting of: an unpaired spin atom, a free radical, a paramagnetic contrast agent and a metal chelate.

3. **(Previously Presented)** A targeted oligonucleotide construct as in claim 1, wherein said imaging agent is a paramagnetic contrast agent selected from the group consisting of: gadolinium, cobalt, nickel, manganese, and iron.

4. **(Previously Presented)** A targeted oligonucleotide construct as in claim 1, wherein the oligonucleotide is an antisense oligonucleotide or an antisense oligonucleotide analog that is modified to enhance its efficacy, pharmacokinetic properties, or physical properties.

5. **(Previously Presented)** A targeted oligonucleotide construct as in claim 1, wherein said imaging agent is a radiolabel selected from the group consisting of: $^{131}I$, $^{123}I$, $^{99m}Tc$, $^{18}F$, $^{68}Ga$, $^{67}Ga$, $^{72}As$, $^{89}Zr$, $^{64}Cu$, $^{62}Cu$, $^{111}In$, $^{203}Pb$, $^{198}Hg$, $^{11}C$, $^{97}Ru$, and $^{201}Tl$.

6. **(Previously Presented)** A targeted oligonucleotide construct as in claim 5, wherein the radiolabel is a chelate.

7. **(Previously Presented)** A targeted oligonucleotide construct as in claim 1, wherein said imaging agent is an iron, lanthanide or gadolinium unpaired spin atom or free radical.

8. **(Previously Presented)** A targeted oligonucleotide construct as in claim 1, further comprising a therapeutic agent.

9. **(Cancelled)**

10. **(Previously Presented)** A targeted oligonucleotide construct as in claim 8, wherein the therapeutic agent is selected from an enzyme, an enzyme inhibitor, a receptor ligand, a radioisotope, an antibiotic, a steroid, a hormone, a polypeptide, a glycopeptide, a phospholipid, and a drug.

11. **(Previously Presented)** A targeted oligonucleotide construct as in claim 8, wherein the oligonucleotide is an antisense oligonucleotide or an antisense oligonucleotide analog that is modified to enhance its efficacy, pharmacokinetic properties, or physical properties.

Claims 12-24 **(Cancelled)**

25. **(Previously Presented)** A targeted oligonucleotide construct as in claim 4, wherein the oligonucleotide is an antisense oligonucleotide analog that is selected from the group consisting of: an antisense oligonucleotide that is modified with a cell uptake facilitating moiety, an antisense oligonucleotide that is modified with a stabilizing moiety, an antisense oligonucleotide that is modified to enhance its solubility, and an antisense oligonucleotide that is modified to enhance its resistance to nuclease digestion.

26. **(Previously Presented)** A targeted oligonucleotide construct as in claim 4, wherein the oligonucleotide is an antisense oligonucleotide analog derivatized with a moiety selected from the group consisting of: biotin, amino glycoside, lipophilic, phosphorothioate, morpholino and deoxy.

27. **(Previously Presented)** A targeted oligonucleotide construct as in claim 4, wherein the oligonucleotide is an antisense oligonucleotide analog derivatized with a phosphorothioate moiety.

28. **(Previously Presented)** A targeted oligonucleotide construct as in claim 4, wherein the oligonucleotide is an antisense oligonucleotide or an antisense oligonucleotide analog that is specific to mRNA.

29. **(Previously Presented)** A targeted oligonucleotide construct as in claim 4, wherein the oligonucleotide is an antisense oligonucleotide or an antisense

oligonucleotide analog that is specific to a gene selected from the group consisting of : C-myb, N-myc, C-myc and PSA gene specific antisense.

30. **(Previously Presented)** A targeted oligonucleotide construct as in claim 11, wherein the oligonucleotide is an antisense oligonucleotide analog that is selected from the group consisting of: an antisense oligonucleotide that is modified with a cell uptake facilitating moiety, an antisense oligonucleotide that is modified with a stabilizing moiety, an antisense oligonucleotide that is modified to enhance its solubility, and an antisense oligonucleotide that is modified to enhance its resistance to nuclease digestion.

31. **(Previously Presented)** A targeted oligonucleotide construct as in claim 11, wherein the oligonucleotide is an antisense oligonucleotide analog derivatized with a moiety selected from the group consisting of: biotin, amino glycoside, lipophilic, phosphorothioate, morpholino and deoxy.

32. **(Previously Presented)** A targeted oligonucleotide construct as in claim 11, wherein the oligonucleotide is an antisense oligonucleotide analog derivatized with a phosphorothioate group.

33. **(Previously Presented)** A targeted oligonucleotide construct as in claim 11, wherein the oligonucleotide is an antisense oligonucleotide or an antisense oligonucleotide analog that is specific to a gene selected from the group consisting of : C-myb, N-myc, C-myc and PSA gene specific antisense.

34. **(Previously Presented)** A targeted oligonucleotide construct as in claim 11, wherein the oligonucleotide is an antisense oligonucleotide or an antisense oligonucleotide analog that is specific to mRNA.

## REMARKS

Claims 1-9, 10, 11 and 25-34 are pending in the application. Claim 1 has been amended. Support for the amendment "wherein said targeted oligonucleotide construct has essentially no ability to cross the blood/brain barrier" may be found at page 46, last paragraph of the specification.

No new matter has been added by the present amendments. The amendments are being made not only to point out with particularity and to claim the present invention, but also to expedite prosecution of the present application. Applicants reserve the option to prosecute the pending claims further, or other ones, in the instant or a subsequent patent application.

Applicants thank Examiner for removing the rejections in the last Office Action.

## CLAIM REJECTIONS

### *Rejection of claims under 35 U.S.C. § 102(b) over Kobori et al. and Pardridge et al.*

The Examiner has rejected claims 1, 4, 5, 8, 11, 25-28, 30-32 and 34 over Kobori et al. (NeuroReport 1999 vol. 10, pages 2971-2974) and claims 1, 4, 5, 8, 10, 11, 25, 26, 28, 30, 31 and 34 over Pardridge et al. (Proc. Natl. Acad. Sci. USA 1995, vol. 92, pages 5592-5596).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Both of the applied references describe constructs that have the ability to cross the blood/brain barrier. Applicants respectfully draw Examiner's attention to page 46 of the specification, which details how the constructs disclosed in the instant specification did not show any appreciable ability to cross the blood/brain barrier. Applicants have amended claim 1 to clarify this property of the constructs. The remaining rejected claims are dependent from claim 1. Therefore, the instantly claimed invention is not anticipated by either the Kobori or the Pardridge reference. Applicants respectfully request reconsideration and withdrawal of the present rejections.

***Rejection of claims under 35 U.S.C. § 103(a) over primary reference Kobori et al.***

The Examiner has rejected claims 1, 4, 5, 8, 11, 25-28, 30-32 and 34 as obvious over Kobori et al. (NeuroReport 1999 vol. 10, pages 2971-2974) and claims 1, 4, 5, 9, 11 and 25-34 over Kobori et al. in view of Gewirtz et al. (U.S. 5,098,890) and Low et al. (U.S. 5,994,320).

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g., Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985). Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations (M.P.E.P. 2143).

The Examiner has not set forth any motivation to combine these references and hence has not established a *prima facie* case of obviousness. Moreover, even if there were motivation to combine the references, the combination does not teach or suggest each and every element of the claims.

Specifically, the Examiner has rejected claims 1, 4, 5, 9, 11 and 25-34 over Kobori et al. in view of Gewirtz et al. (U.S. 5,098,890) and Low et al. (U.S. 5,994,320). As discussed above, Kobori et al. describes constructs that have the ability to cross the blood/brain barrier. The instantly claimed constructs have little, if no, ability to cross the blood/brain barrier. Gerwitz et al. and Low et al. do not teach or suggest how the constructs of Kobori may be modified so that they do not cross the blood/brain barrier. Accordingly, the combination does not teach or

suggest each and every element of the claims, and the Examiner has not established a *prima facie* case of obviousness using these references.

Further, the Examiner has rejected claims 1, 4, 5, 8, 11, 25-28, 30-32 and 34 as obvious over Kobori et al. (NeuroReport 1999 vol. 10, pages 2971-2974). As discussed above, Kobori et al. describes constructs that have the ability to cross the blood/brain barrier. The instantly claimed constructs have little, if no, ability to cross the blood/brain barrier. One of skill in the art would not be motivated to modify Kobori to produce a construct that exhibits a *reduced* ability to cross the blood/brain barrier, because the blood/brain barrier strictly limits the ability of most agents to cross from the blood to the brain and very few effective delivery systems exist for the delivery of therapeutic molecules across this barrier. Accordingly, one of skill in the art would not be motivated to so modify Kobori in view of the art.

Applicants respectfully request reconsideration and withdrawal of the present rejections.

## CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims now pending are in condition for allowance, and notification of such is respectfully requested.

If, for any reason, a telephonic conference with the Applicants would be helpful in expediting prosecution of the instant application, the Examiner is invited to call Applicants' Agent at the telephone number provided below.

Respectfully submitted,
FOLEY HOAG LLP

October 24, 2005

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